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| 10/669,540 | 09/23/2003 | Robert Terkeltaub | UCSD1570-1 | 4639 |

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| EXAMINER | |
|---|---|
| EMCH, GREGORY S | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/669,540 | TERKELTAUB, ROBERT | |
| | Examiner | Art Unit | |
| | Gregory S. Emch | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 February 2008 and 21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3 and 5-14* is/are pending in the application.

4a) Of the above claim(s) *7 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3 and 5-14* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

Claim 1 has been amended, and claim 15 has been canceled as requested in the amendment filed on 21 February 2008. Following the amendment, claims 1-3 and 5-14 are pending in the instant application.

Claims 7 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim.

Claims 1-3, 5, 6 and 8-13 are under examination in the instant office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

### *Information Disclosure Statement*

A signed and initialed copy of the IDS paper filed on 21 April 2008 is enclosed in this action.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5, 6 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al. and Oliverio et al. (citation O on IDS dated 24 November 2004), further in view of Heyninck et al. and Grey et al (citation G on IDS dated 24 November 2004).

Claims 1, 2, 3, 5, 6 and 8-10 are directed to a method for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: contacting the cartilage matrix of a subject in need thereof with an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix, wherein the inhibitor is A20 or NG-monomethyl-L-arginine acetate (NMMA), thereby suppressing pathological calcification in the cartilage matrix. Claims 11-13 are directed to a method for identifying an agent that inhibits matrix calcification, comprising contacting a chondrocyte in vitro with a test agent under conditions for inducing matrix calcification, wherein the chondrocyte expresses zymogen factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase); and determining the effect of the test agent on activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage matrix, wherein

inhibition of activation and/or activity is indicative of a test agent that inhibits matrix calcification.

The Nurminskaya et al. reference teaches that transglutaminase and FXIIIa are unregulated during chondrocyte hypertrophy and calcification (p.1135) and that these factors are implicated in apoptotic cell death mechanisms in chondrocytes (e.g., p.1136, ¶3, p.1142, ¶5), as in the instant claims 1 and 5. Further, the Nurminskaya et al. reference teaches chondrocytes from a chondrocyte-derived cell line (p.1136, ¶5), as in the instant claims 10 and 13. Although the teachings of Nurminskaya et al. suggest that blocking activation or activity of tTGase and FXIIIa would decrease apoptosis in pathological states, the reference does not explicitly teach such.

Upon reading the disclosure of the Nurminskaya et al. reference, the skilled artisan would have recognized the desirability of developing improved methods for treating pathological calcification of the cartilage matrix. Furthermore, the Hashimoto et al. reference teaches that articular and meniscal chondrocyte apoptosis and abnormal articular cartilage matrix calcification and degradation are involved in human osteoarthritis (pp.1632-1633), as in the instant claim 1. The Hashimoto et al. reference also teaches that future treatment options, (e.g., apoptotic inhibitors), would alleviate chondrocyte apoptosis and thus matrix calcification and degradation (p.1638, final paragraph). The Hashimoto et al. reference teaches that mediators of necrosis and apoptosis in chondrocytes include IL-1, TNFα and nitric oxide (p.1632, ¶3), as in the instant claim 2. Both references teach *in vitro* and *in vivo* methods (entire documents), as in the instant claims 8 and 9, and both references utilize expression vectors to

express FXIIIa in chondrocytes (e.g., Nurminskaya et al., p.1137, ¶5, as in the instant claims 12 and 13. Also, the Oliverio et al. reference teaches that inhibition of tTGase increases cell survival by preventing apoptosis and teaches *in vitro* assay methods whereby U937 cells that express tTGase are exposed to agents that inhibited apoptosis and tTGase (entire document, e.g. abstract and p.34125, Fig. 2C), as in claim 11. Moreover, the Heyninck et al. reference teaches that the TRAF2 mediated NF-κB signal transduction pathway is implicated in apoptosis (p.1472, column 1) and teaches that cellular expression of A20 inhibits TRAF2 mediated NF-κB signal transduction in human embryonic kidney cells (entire document, e.g. abstract), as in the instant claims 3, 5 and 6. Further, the Grey et al. reference teaches that A20 inhibits cytokine-induced apoptosis and NF-κB activation in islet β cells (entire document, e.g., abstract).

As evidenced by the prior art, the skilled artisan would have known that inhibiting tTGase and FXIIIa and TRAF2 mediated NF-κB signal transduction to reduce apoptosis would alleviate disorders of pathological calcification and degradation of the cartilage matrix. Furthermore, it would have been reasonable to predict that A20 would have successfully treated pathological calcification of cartilage given the teachings of Nurminskaya et al. and Hashimoto et al. that inhibition of apoptosis is an appropriate therapeutic approach, and the teachings of Heyninck et al. and Grey et al. that A20 is such an apoptosis inhibitor. Thus, it would have been obvious to the person of ordinary skill to try administration of A20 in an attempt to provide an improved method of treating such disorders and to try to identify agents that affect matrix calcification, (as the instant

claim 11), as taught by Hashimoto et al. (p.1638, final paragraph). This is because the artisan has good reason to pursue the known options within his or her technical grasp.

In the reply filed on 21 February 2008, regarding the previous rejection under 35 U.S.C. 103(a), Applicant asserts that use of A20 as an inhibitor to suppress pathological calcification in the cartilage matrix was not a known option within the artisan's technical grasp. Applicant asserts that Heyninck's disclosure of A20 as an inhibitor of TNF-induced NF-κB activation would not lead one of skill in the art to conclude that A20 would effectuate inhibition of apoptosis in chondrocytes. Applicant asserts that Heyninck discloses that NF-κB signal transduction is cell-type dependent and implicates a variable role of A20 in different cell types. Applicant asserts that the authors disclose that "stable expression of A20 has been reported to be unable to prevent TPA- induced NF-κB activation in breast carcinoma MCF cells" (page 1479, column 2, last paragraph). Applicants assert that from the disclosure of Heyninck, the skilled artisan would conclude that induction of apoptosis is cell-type dependent and inhibition of NF-κB activation is dependent on how NF-κB activation is induced. Applicant directs the Office to Exhibits 1-5, submitted on the IDS dated 21 April 2008, to show that it is well settled in the art that the induction of apoptosis, as well as inhibition thereof, is cell type dependent. Applicant asserts that in light of the disclosure of Heyninck and knowledge in the art, the skilled artisan would not have known how apoptosis is induced in chondrocytes and how to inhibit apoptosis in such a cell. Applicant asserts that none of the cited references disclose or even hint at an *in vitro* method of identifying inhibitors of

matrix calcification, by determining a test agent's effect on the activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage matrix. Applicant asserts that relying on the cited art, a skilled artisan would not have known whether inhibition of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage matrix would inhibit matrix calcification. Applicant asserts that none of the cited references clearly establish such an association beyond conjecture.

Applicants' arguments have been fully considered and are not found persuasive. Regarding Applicant's assertion that Heyninck's disclosure of A20 as an inhibitor of TNF-induced NF-κB activation would not lead one of skill in the art to conclude that A20 would effectuate inhibition of apoptosis in chondrocytes, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of the prior art references of record that renders the claims obvious. The Heyninck et al. reference teaches that the TRAF2 mediated NF-κB signal transduction pathway is implicated in apoptosis (p.1472, column 1) and that cellular expression of A20 inhibits this signal transduction in HEK cells. It is this information in combination with the disclosure of the Nurminskaya et al. reference, i.e. that tTGase and FXIIIa are implicated in apoptotic cell death mechanisms in chondrocytes, which would lead the artisan to conclude that A20 would cause inhibition of apoptosis in chondrocytes. This is also supported by the Grey et al. reference, which teaches that A20 inhibits cytokine-

induced apoptosis and NF-κB activation in islet β cells (entire document, e.g., abstract), and the Oliverio et al. reference, which teaches that inhibition of tTGase increases cell survival by preventing apoptosis. Thus, Applicant's arguments and extrinsic evidence (i.e., the prior art references referred to as Exhibits A-E) that allegedly support the assertion that induction and inhibition of apoptosis are cell type dependent would not deter the artisan from concluding that A20 could be used as inhibitor of apoptosis (and of tTGase and FXIIIa activation). Given the teachings of Nurminskaya et al. and Hashimoto et al. that inhibition of apoptosis is an appropriate therapeutic approach to treat pathological calcification of cartilage, and given the teachings of Heyninck et al. and Grey et al. that A20 is such an apoptosis inhibitor, it would have been reasonable to predict that A20 would have successfully treated pathological calcification of cartilage. Thus, the artisan would at least be motivated to try such a treatment approach, and contrary to Applicant's argument that use of A20 as "an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix" to suppress pathological calcification in the cartilage matrix, was indeed a known option within the artisan's technical grasp.

Applicant's assertion that none of the references disclose or hint at an *in vitro* method of identifying inhibitors of matrix calcification is inaccurate. The references strongly suggest such a method. The Nurminskaya et al. reference implicates tTGase and FXIIIa in apoptotic cell death mechanisms in chondrocytes. The Oliverio et al. reference confirms that inhibition of tTGase increases cell survival by preventing apoptosis and teaches *in vitro* assay methods whereby U937 cells that express tTGase

are exposed to agents that inhibited apoptosis and tTGase. Further, the Hashimoto et al. reference teaches that articular and meniscal chondrocyte apoptosis and abnormal articular cartilage matrix calcification and degradation are implicated in human osteoarthritis and that future treatment options, (e.g., apoptotic inhibitors), would alleviate chondrocyte apoptosis and thus matrix calcification and degradation. Applicant is reminded that "specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involve not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art." See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY 1979); and In re Burckel 201 USPQ 67 (CCPA 1979).

***Conclusion***

No claims are allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

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27 June 2008

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